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EDITORIAL COMMENT

Anthracycline-Induced Cardiotoxicity

Remembering the Forgotten Ventricle*

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Since the 1960s, anthracyclines have been an integral part of cancer treatment, and they remain as first-line therapy for a wide variety of solid tumors and hematological malignancies, including breast cancer, lymphoma, leukemia, and sarcoma. However, dose-related cardiotoxicity presenting as left ventricular (LV) systolic dysfunction with or without symptomatic heart failure is a limiting factor in the use of this highly effective chemotherapeutic agent. The cumulative incidence of cardiac events has been estimated at 32%, 54%, and 65% for cumulative doxorubicin doses of 400, 500, and 550 mg/m^2 (1). Clinical evidence of cardiotoxicity may become apparent within 1 to 2 years after treatment but can also manifest years later. Long-term follow-up data from the Childhood Cancer Survivorship Study showed that adult survivors of childhood cancer treated with anthracyclines were 5 to 6 times as likely as their siblings to experience heart failure (2).

Anthracyclines induce ultrastructural changes in the cardiomyocyte that lead to cellular apoptosis and necrosis. Early animal and human studies have suggested that the cardiotoxic effect of anthracyclines provokes global injury extending to both the left and right ventricles (3). The phenotype of anthracycline-induced cardiomyopathy is characterized by impairment of systolic and diastolic function with thinned walls and a normal or dilated LV cavity size. Given the poor prognosis of advanced heart failure, many efforts have focused on cardiac monitoring because early detection of cardiac injury may facilitate timely therapeutic measures and mitigate cardiac damage. Two-dimensional (2D) transthoracic echocardiography (TTE) has been the mainstay of imaging for the assessment of cardiac function and detection of cardiotoxicity during cancer treatment (4). Thus far, attention has been directed to the left side of the heart, particularly LV ejection fraction and strain. Myocardial strain imaging is often incorporated into monitoring for detection of subclinical LV dysfunction. Right ventricular (RV) dysfunction, however, has not been considered in the definition of cardiotoxicity. There have been limited investigations into the effects of cancer chemotherapy on RV function and remodeling. The incidence and prognosis of RV dysfunction during cardiotoxic treatment are largely unknown. Until recently, the right ventricle had been relatively neglected, mainly due to the technical challenges in the accurate assessment of the complex crescent-shaped right ventricle by 2D TTE plus the impression that it may not be as important in cardiovascular disease.

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Advanced echocardiographic techniques such as three-dimensional TTE and strain imaging have led to an improved assessment of RV anatomy and function (5). This modality has emerged as a valuable tool providing critical information regarding the unique physiological properties of the right ventricle in health and disease. Multiple studies have now shown the incremental value of RV function over clinical risk factors and other parameters of LV dysfunction for predicting outcome in patients with various cardiovascular pathologies (6). In this issue of *JACC: CardioOncology*, Zhao et al. (7) reported their investigation using 2D and 3-dimensional (3D) TTE with

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strain imaging to describe the sequence of changes in RV size and function in patients with lymphoma during the course of their doxorubicin-based chemotherapy. The results showed an increase in RV end-systolic and end-diastolic volume followed by a decrease in RV ejection fraction (RVEF), as well as a worsening in RV strain over time. There was a concurrent worsening in LV global longitudinal strain but no change in LV volume or left ventricular ejection fraction (LVEF) during the follow-up period. The study identified changes in RV end-systolic volume and RV free wall longitudinal strain as predictors of RV cardiotoxicity defined by a reduction in RVEF from baseline.

This paper (7) adds to the existing literature and further informs our understanding of the impact of anthracycline therapy on the right ventricle. Although a few studies have shown a decline in RV function during cancer treatment (8), this study found that RV remodeling and functional impairment occurred before any changes in LVEF or LV volume. This is an important finding not previously reported, suggesting the possibility that the right ventricle may be affected earlier than the left ventricle. Given its distinct morphological features and myofiber architecture, the right ventricle could conceivably be more vulnerable than the left ventricle to injury. It is intuitive that the thinner RV walls with fewer myofibrils may be more sensitive to the toxic effects of chemotherapy than the thicker, more muscular left ventricle. Furthermore, the RV free wall is composed predominantly of longitudinally arranged, apex to base subendocardial fibers that account for the majority of RV pump function under normal conditions (9). The subendocardial layer of the myocardium, responsible for the longitudinal shortening, has been shown to be most vulnerable to the toxic effects of chemotherapy in histological studies (10). Unlike the left ventricle, the mid-layer containing circumferential fibers in the RV myocardium is absent and thus cannot compensate for the loss of longitudinal shortening of the subendocardial fibers. Thus, longitudinal shortening assessed by strain imaging should have the potential to detect early changes in RV myocardial dysfunction. The current study detected impairment of longitudinal strain of the RV free wall before RVEF decline which can be explained by RV mechanics. However, whether impairment occurs in the right ventricle before the left ventricle warrants further evaluation.

There are several limitations to the study by Zhao et al. (7). The most important one is the lack of follow-up data to place the RV changes in context. Studies have shown that long-term adult survivors of childhood cancers treated with anthracyclines have impaired RV function or reduced functional reserve during exercise compared with matched control subjects (11,12). It would be important to establish if changes in RV function in the current study persist over time or predict subsequent declines in LVEF or heart failure. Another limitation is that the RV remodeling observed may still be related to fluctuations in pre-load, even though the volume status was deemed stable, as even a small change in fluid status could lead to a modest change in RV volume. Re-measuring the RV parameters after therapy and stabilization would help clarify and confirm the presence of RV dysfunction. Furthermore, the clinical significance of "RV cardiotoxicity" is unknown as it was arbitrarily defined based on a relative change in RVEF. Whether RV dysfunction assessed by echocardiography is associated with any adverse clinical outcome requires further evaluation. Finally, this was a small single-center study, and the validity of the findings must be confirmed in larger studies. Ideally, cardiac magnetic resonance imaging, the reference standard for RV volume and function assessment, at baseline and end of therapy, would improve the reliability of the observations. The addition of tissue characterization by cardiac magnetic resonance imaging, such as myocardial edema and inflammation, could provide further insight into the underlying histopathological myocardial changes (13).

Despite the uncertain impact of these findings, this study (7) should be recognized for expanding the application and feasibility of 3D TTE for cardiotoxicity monitoring in patients during cancer treatment. Previous studies have reported abnormalities in 3D LV mechanics in anthracycline-induced cardiotoxicity (14). This study provides novelty with measurement of 3D RV mechanics and volume in patients receiving anthracycline treatment. However, whether 3D TTE is a viable modality to monitor RV structure and function outside the research setting remains to be seen. Longitudinal studies are needed to assess the impact of echocardiography-derived indices of RV function on prognostic outcome and whether they represent clinically meaningful markers of cardiotoxicity that should be incorporated as part of cardiotoxicity monitoring during cancer therapy.

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